IN THE SPECIFICATION:

Please amend the specification as follows:

On page 1, immediately following the title, please insert the following sentence:

This is a national phase of PCT/GB03/02420 filed June 2, 2003 and published in English.

Please replace the paragraphs beginning at page 12, line 12 through page 14, line 17 with the following rewritten paragraphs.

-- Figure 6 shows a LC/ES-MS analysis of lysine terminal standard peptides treated with O-methyl isourea. Selected ion monitoring (SIM) of four marker-ions is performed selecting the singly and doubly charged ions of lysine (K) and its corresponding homoarginine terminal peptide (K*), (a) 35 pmole of interleukin $[M+2H]^{2+}$ and $[M+H]^{+}$ at 503.2 and 1005.4 are indicated with 2+ and 1+ respectively. (b) 50 pmole of AFLDASK (SEQID NO: 1) $[M+2HF]^{2+}$ and $[M+H]^{+}$ at

376.25 and 751.25 are indicated with 2+ and 1+ respectively. The arrows indicate the expected retention times of the unmodified lysine containing peptides;

Figure 7 shows a LC/ES-MS analysis of an equimolar mixture of interleukin (K, 12.5pmole) with its guanidinated counterpart (K*,12.5pmole) acquired in selected ionmonitoring. Doubly charged ion signals are indicated with +2 while singly charged ion signals correspond to +1, (b) SIM LC/ES-MS analysis of a equimolar mixture of 20 pmole of AFLDASK (SEQID NO: 1) with AFLDASK* (SEQID NO: 2);

Figure 8 shows a LC/ES-MS analysis of a solution containing equal amount (15 pmole) of ALFDASK (SEQID NO. 1), AFLDASR (SEQID NO: 3) and the homoarginine terminal analogue AFLDASK* (SEQID NO: 2). The lysine terminal peptide is eluted first followed by the arginine terminal counterpart. SIM analysis of all six ions indicates

that the homoarginine terminal peptide ions are the dominant signals in the MS chromatogram regardless of the charge state selected;

Figure 9 shows an isocratic separation of a solution containing equal amount (31.5pmole) of AFLDASK (SEQID NO: 1), AFLDASR (SEQID NO: 3) and the AFLDASK* (SEQID NO: 2). The conditions employed correspond to the concentration of mobile phase (0.05% (v/v) TFA and 32.6% (v/v) acetonitrile) at which the peptides were eluted in gradient mode;

Figure 10 shows a series of target modules;

Figure 11 shows the derivatisation of AFLDASK (SEQID NO: 1) with target A. The ion signal [M+H] + at m/z 1019 corresponds to the mono-adduct produced by the reaction between target A and the lysine terminal peptide AFLDASK (SEQID NO: 1);

Figure 12 shows the derivatisation of AFLDASK (SEQID NO: 1) with 1-acetyl-2-methyl isourea. The ion at m/z 835.2 is the mono-adduct produced by coupling between AMIU and the lysine terminal peptide;

Figure 13 shows a PSD MALDI TOF spectrum of the ion corresponding the peptide derivatised with target A;

Figure 14 shows a PSD MALDI TOF spectrum of the AFLDASK (SEQID NO: 1) peptide derivatised with target B (AMIU);

Figure 15 shows a PSD MALDI TOF spectrum of the AFLDASK (SEQID NO: 1); and

Figure 16 shows a MALDI spectra of AFLDASK (SEQID NO: 1) differentially labelled.

Please replace the paragraphs beginning at page 22, line 15 with the following rewritten paragraphs.

Interleukin, VQGEESNDK (SEQID NO: 4) (Sigma), AFLDASR (SEQID NO: 3) and AFLDASK (SEQID NO: 1) with purity >96% (New England Peptide Inc) were used in concentrations of 2-20 pmol/µl. All experiments were performed on a single quadruple mass spectrometer LCMS-2010 (Shimadzu, Japan) fitted with an electrospray source. Source conditions were maintained constant during the analysis. Data was acquired in selected ion monitoring mode (SIM) for a total of twelve selected ions. Components were separated on a Phenomenex Luna C_{18} column (2.0mm id x 50mm). In gradient mode, mobile phase composition was 0.05% TFA (v/v) for the aqueous phase and acetonitrile/water (9:1 v/v) incorporating 0.05% TFA (v/v) for the organic phase. LC10ADVp HPLC pumps (Shimadzu, Japan) were used to deliver solvent at a flow rate of 250µl/min.

Please replace the paragraph beginning at page 23, line 16 through page 25, line 9 with the following rewritten paragraph.

The completeness of guandination allows preparation of homoarginine terminal peptide solutions with known concentrations. Binary mixtures containing the same quantity of lysine terminal peptide and its analogous homoarginine terminal counterpart were prepared and a comparison between the two ion signals is performed. Figure 7a shows an MS chromatogram of 20 pmole of interleukin with its guanidinated analogue during LC separation followed by ES. The

conditions employed during the chromatographic separation (composition of mobile phases, gradient profile, etc) were kept identical to those used in the previous experiment (see Figure 6). Total ion chromatogram (TIC) traces of homoarginine terminal peptides (corresponding to the sum of the singly and doubly charged ion signals) have higher relative intensity than lysine terminal ones. The main contribution is due to the relative ES response of the doubly charged ion peaks. This observation is also made with an equimolar mixture of AFLDASK (SEQID NO: 1) with its guanidinated counterpart AFLDASK* (SEQID NO: 2) (Figure 7B).

LS-MS analysis of a mixture containing AFLDASK (SEQID NO: 1), AFLDASR (SEQID NO: 3) and its homoarginine terminal counterpart AFLDASK* (SEQID NO: 2).

To investigate how minor variations in peptide structure may affect signal intensity, the arginine terminal analogue AFLDASR (SEQID NO: 3) was added to the mixture. Figure 8 indicates the ion chromatograms of a solution containing 31.5 pmole each of AFLDASK (SEQID NO: 1), AFLDASR (SEQID NO: 3) and the homoarginine terminal derivative AFLDASK* (SEQID NO: 2) separated by LC prior to MS detection. The arginine terminal peptide displays an ion chromatogram with intensity higher than the corresponding AFLDASK (SEQID NO: 1) in accordance with the higher basicity of the arginine. By comparing the two sets of peptide ions produced by

AFLDASR (SEQID NO: 3) and AFLDASK* (SEQID NO: 2), the latter one generally displays ion signals with higher intensity. Unlike the lysine and arginine/ homoarginine terminal peptides (AFLDASK (SEQID NO: 1) vs AFLDASR SEQID NO: 3/AFLDASK* (SEQID NO: 2)) where the difference in ionisation efficiency can be related to the higher stabilisation of the protenated peptide, in the case of the AFLDASK (SEQID NO: 1) and AFLDASK* (SEQID NO: 2) the difference in ES response cannot be simply related to the effect of the guanidino group as both are identical. The difference can be attributed to the increased level of proton solvation provided by the extra methylene group in the peptide backbone.

Effect of isocratic separation on ESI response of AFLDASK (SEQID NO: 1), AFLDASR (SEQID NO: 3) and AFLDASK* (SEQID NO: 2) peptide ions.

The effect of co-elution of three peptides on their ESI response was studied. The mixture previously analysed (see Figure 8) was run isocratically. The mobile phase was prepared with the same composition used to elute AFLDASR (SEQID NO: 3), AFLDASK (SEQID NO: 1) and AFLDASK* (SEQID NO: 2) in the gradient mode. Hence, no separation is achieved and all three peptide elute simultaneously into the mass spectrometer. None of the ion signals in the MS chromatogram are suppressed compared with the ion signals observed

in the LC-MS experiment (see Figure 8). The co-presence of three peptides different in gas/phase basicity shows no effect on their ESI response. Figure 9 displays MS chromatograms of AFLDASK (SEQID NO: 1), AFLDASR (SEQID NO: 3) and AFLDASK* (SEQID NO: 2) for singly and doubly charged protonated ions.

Please replace the paragraphs beginning at page 26, line 4 through page 27, line 4 with the following rewritten paragraphs.

The reactions between the newly synthesised compounds, A,B and a standard peptide (AFLDASK (SEQID NO: 1)) were tested by using 100 pmole of peptide. Experiments were performed to assess the reactivity of Target A (Figure 11) and Target B (Figure 12) with lysine terminal peptides. MALDI analysis was used to evaluate the purity of these compounds. Only one ion signal corresponding to the derivatised peptide is present in the MALDI spectrum. From the analysis performed, it can be assumed that the reaction is quantitative and no starting material is left in the reaction mixture. Additionally, the presence of just one main ion peak in each spectrum rules out the possibility of the multiple derivatisation due to the amino group at N-terminus.

MS/MS analysis of the derivatised AFLDASK (SEQID NO: 1)

Since the N-terminal amino group could interfere with the reaction, tandem mass spectrometric analysis was conducted on the derivatised ions. The product ion spectra were found to demonstrate that the y ions are affected by a shift due to the reaction occurring between the lysine amino group and the reagent. No evidence of coupling on N-terminus was found. MS/MS analysis was performed by exploiting the natural decomposition of the ions in the free-field region of the time-of-flight instruments (PSD). Figure 13 shows the MS/MS spectrum of the derivatised AFLDASK (SEQID NO: 1) with Target A. y ions dominate the spectrum and are shifted by 268 amu. Similarly the product ion spectrum of the reaction between AFLDASK (SEQID NO: 1) and AMIU illustrates a similar trend (Figure 14). Figure 15 illustrates the fragmentation pattern of the underivatised AFLDASK (SEQID NO: 1).

MALDI spectra of differentially labelled lysine terminal peptides

Figure 16 displays the spectra of AFLDASK (SEQID NO: 1) labelled with Target B (lower spectrum) and Target D (upper spectrum). As expected the difference in mass between the two peptide ions is 5 Daltons.